Chapter 1

Bimetallic catalysis by late transition metal complexes

1.1 Introduction

Homogeneous catalysis is one of the most rapidly evolving areas of synthetic organic chemistry. Due to the strong incentives to achieve environmentally friendly, high-economy processes much research is performed to develop better and more selective catalysts.[1] Until now, the most selective catalysts are found in nature. Due to improved spectroscopic techniques, the elucidation of the structure of the active sites of many enzymes and the nature of the key intermediates in enzyme catalyzed processes has seen dramatic progress in recent years. It has been shown that a number of these active sites contains two metal ions, that operate cooperatively.[2] As a result, dinuclear complexes containing two metals in close proximity have become the subject of extensive investigations in order to design new bimetallic catalysts.[3]

Complexes of interest for mimicking activity of enzymes are especially dinuclear copper and iron compounds designed for reversible binding of dioxygen or activation of dioxygen. For instance, the dinuclear copper active site of hemocyanin[4] can reversibly bind dioxygen. The enzyme tyrosinase[5,6] can activate dioxygen and hydroxylate monophenols to catechols and further oxidize these catechols to *o*-quinones. Enzymes containing a dinuclear iron active site are hemerythrin,[7] methane monooxygenase[8,9] and ribonucleotide reductase.[9,10] Hemerythrin is an dioxygen carrier and methane monoxygenase and ribonucleotide reductase activate dioxygen to hydroxylate methane to methanol and to generate a tyrosyl radical, respectively.

Furthermore, many enzymes that contain two manganese ions in their active site have been discovered.[11] However, the mechanisms of these enzymes are until now poorly understood. The reactions that are catalyzed show wide variety, including several redox types, such as oxygen atom transfer, reduction of ribonucleotides to deoxyribonucleotides, or thiosulfate oxidation to sulfate in thiobacilli.

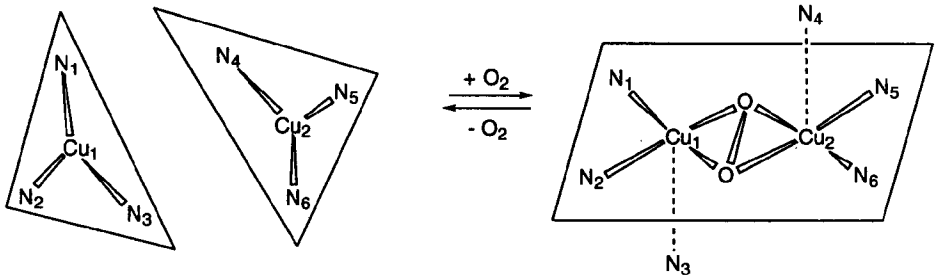
Attempts to mimic features of the active sites of these enzymes resulted in the awareness that two metals can cooperate in catalytic reactions and catalyze the reactions more efficiently or in a different manner than two isolated metal centers.[12] Many dinuclear copper, iron, cobalt and manganese complexes have been synthesized successfully and they have shown a cooperative effect in the activation of dioxygen.[3] Moreover, synthetic dinuclear catalytic sites of transition metal complexes, which are not known to be present in dinuclear active sites of enzymes, have also shown cooperativity of the two metal centers during catalysis. Prominent examples are a dinuclear rhodium complex that has successfully been used in hydroformylation[13] of 1-hexene and a dinuclear palladium complex that catalyzes the hydration reaction of acetonitrile or related organic substrates.[14] For a better understanding of these processes, the study of the interaction of two metals in naturally occuring dinuclear sites (enzymes) and in synthetic dinuclear sites is required.

In this chapter, enzymes with dinuclear active sites as well as complexes mimicking features of these enzymes will be described. Furthermore, recent advances in synthesis and application of dinuclear late transition metal complexes, that show promising bimetallic catalysis, will be discussed.

1.2 Naturally occurring dinuclear active sites

1.2.1 Dinuclear copper enzymes

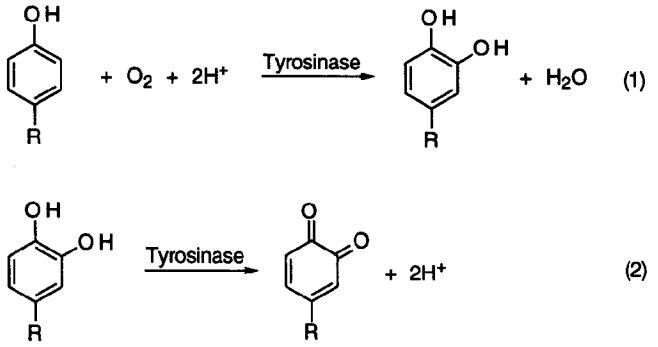
Various enzymes with a dinuclear copper active site are known.[15] A well studied example is *hemocyanin* which functions as a dioxygen carrier in several species of the phyla *Mollusca* and *Anthropoda*.[4] The two copper ions are bound by three histidine imidazole ligands. Upon oxygenation the colorless protein becomes blue (hence *cyanin* from *cyanos*, Greek for blue). Recently, high resolution X-ray structures of hemocyanin from the anthropod *Limulus* in the oxygenated[5] and deoxygenated[16] form have been determined (Scheme 1.1). In the deoxygenated form, the Cu···Cu distance is 4.6 ± 0.2 Å. In the oxygenated form a shorter Cu···Cu distance of 3.6 ± 0.2 Å is found. The closer Cu-Cu distance is presumably required to coordinate the oxygen molecule.
The dioxygen binding of the two copper centers can be described as a change in the oxidation state of the copper ions from Cu(I) to Cu(II) as the dioxygen is bound as O_2^{2-} in a $\eta^2\eta^2$ geometry.[4] In the deoxygenated state, each copper ion has a trigonal coordination by three histidine residues, consistent with the Cu(I) state. In the oxygenated form, the two copper atoms are coordinated by the two oxygen atoms and four nitrogen atoms of the histidines in an approximately square planar geometry.
The hemocyanin dicopper sites are known to coordinate also other compounds besides dioxygen like nitrous oxide and hydrogen peroxide.



Scheme 1.1 Schematic diagrams of the dioxygenated (left) and the oxygenated (right) *Liminus* subunit II hemocyanin dicopper sites.[4]

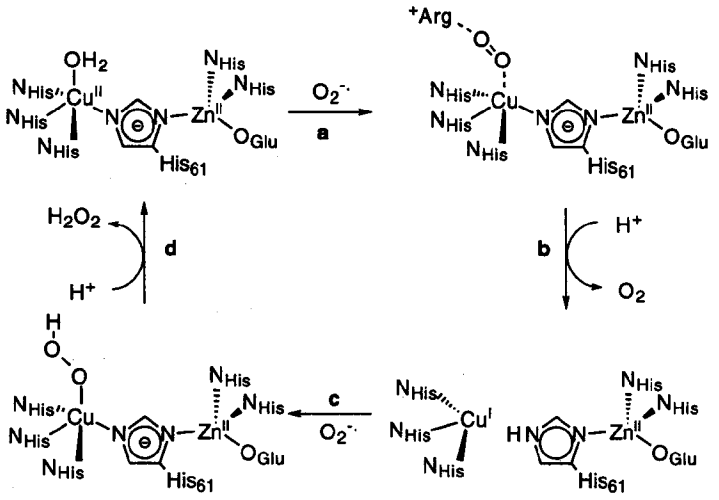
Tyrosinase is an enzyme that is closely related to hemocyanin and belongs to the class of monooxygenases.[5,6] Tyrosinase uses O_2 in the hydroxylation of phenols to *o*-phenols (cresolase activity, reaction 1) and the further oxidation of these *o*-phenols to *o*-quinones (catecholase activity, reaction 2). The active site of tyrosinase consists of a similar structural

unit as hemocyanin, however, the copper centers are less protected by the protein environment.[17]



Scheme 1.2 Cresolase (1) and catecholase (2) activity of tyrosinase.

Another metalloenzyme, *superoxide dismutase*, contains two different metals in its active site: *i.e.* copper and zinc.[18] In the bimetallic region, the copper(II) center is coordinated in a square pyramidal geometry by four histidines and a water molecule. One of the histidines functions as a bridge to the zinc atom and is deprotonated. The zinc atom is further coordinated to two other histidines and one aspartic acid residue in an approximately tetrahedral geometry.

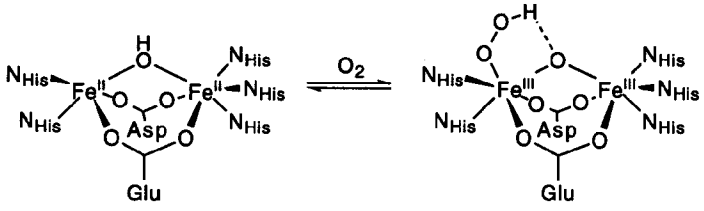


Scheme 1.3 Proposed mechanism for the catalysis of superoxide disproportionation by metalloenzymes.

Superoxide dismutase can destroy the highly reactive, destructive and toxic superoxide radical anion, $O_2^{-\cdot}$ to H_2O_2 and O_2. In the proposed mechanism (Scheme 1.3), the superoxide anion coordinates to the copper ion and to the guanine group of an arginine residue of another peptide chain (**a**). An electron is transferred to the Cu(II) center to form Cu(I) and dioxygen is released upon protonation of the histidine moiety (**b**). Next, a second $O_2^{-\cdot}$ binds to Cu(I) and is protonated (**c**). Transfer of one proton and one electron affords hydrogen peroxide and regenerates the Cu(II) ion (**d**). In this mechanism the zinc ion assists the protein to adopt the required coordination environment. However, it should be noted that there are ambiguities with respect to this mechanism. The turnover of the enzyme is too high for the involvement of protonation and deprotonation of the bridging histidine[19] and, if the zinc ion is removed, there is still dismutation however with only a limited turnover rate.[20]

1.2.2 Dinuclear iron enzymes

Hemerythrin[7] is well known for its function as a dioxygen carrier. The active center consists of two iron atoms roughly 3.25-3.5 Å apart, which are bound to the protein ligand by seven amino acid side-chain residues (Scheme 1.4). Three histidines bind to one iron and two histidines bind to the other iron. Glutamic acid and aspartic acid residues bridge the two metals. Furhermore, an oxygen atom derived from water is bound to both irons. EXAFS[21] and crystallographic studies[22] indicate that in deoxyhemerythrin the oxo bridge is protonated. The two iron atoms are in the Fe(II) state. Upon oxygen binding the colorless deoxyhemerythrin is converted to the purple oxyhemerythrin and the iron atoms are oxidized to Fe(III). At the same time, the proton from the hydroxide bridge migrates to the coordinated oxygen. Molecular oxygen is therefore bound as peroxide with a hydrogen bond to the bridging oxo moiety.



Scheme 1.4 Proposed active site structures of deoxyhemerythrin and oxyhemerythrin.

Methane Monooxygenase (MMO), which consists of three components: a hydroxylase, a reductase and a coupling protein, converts methane to methanol in a process that is coupled to the oxidation of NADH (Scheme 1.5).[9] The diiron site resides in the hydroxylase component (MMOH) and is responsible for oxygen activation and alkane hydroxylation.

$$CH_4 + O_2 + H^+ + NADH \longrightarrow CH_3OH + H_2O + NAD^+$$

Scheme 1.5 Oxidation of methane to methanol by MMO.

The crystal structures of both the oxidized[23] and the reduced form[24] of MMOH have been determined for the *Methylococcus capsulatus* enzyme (Fig. 1.1). The oxidized form contains a dinuclear Fe(III)-Fe(III) center. The two irons are bridged by a glutamate side chain, a hydroxide ion and an acetate ion from the crystallization buffer. The terminal ligands are two histidine nitrogens, three carboxylate oxygen donors and a water molecule that is hydrogen bonded to two carboxylate groups. Upon reduction of the dinuclear iron center to the Fe(II)-Fe(II) form, one specific ligand (Glu 243) undergoes a so called "carboxylate shift" from monodentate terminal ligand to Fe2 to monodentate bridging ligand between the two irons. The other oxygen of the carboxylate group coordinates to Fe2 and the hydroxide bridge is lost. Only the reduced form reacts with dioxygen.

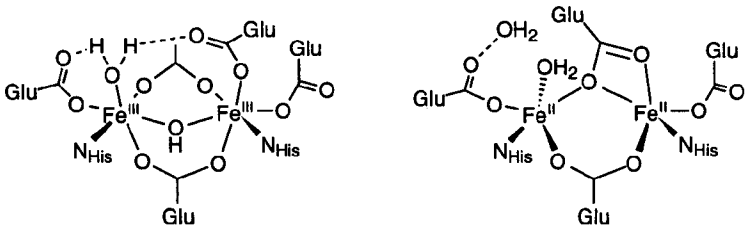
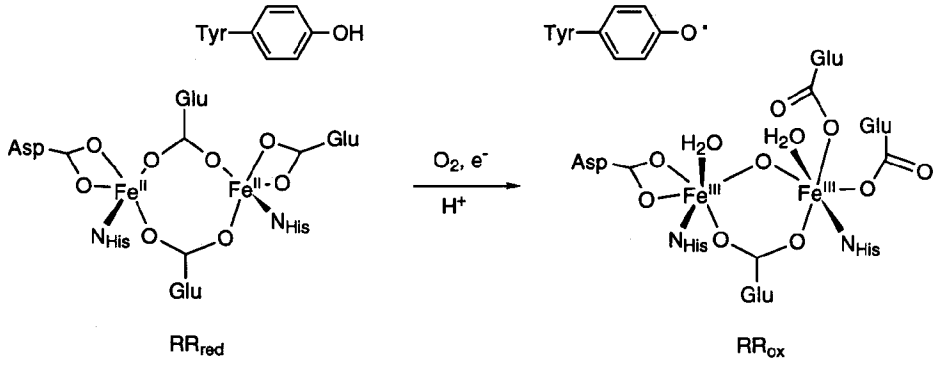


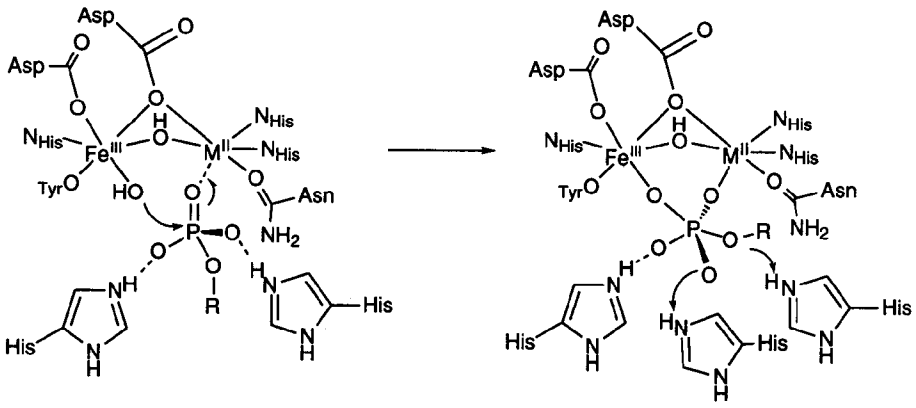
Figure 1.1 Structure of the active site of the oxidized and the reduced form of methane monooxygenase.

Ribonucleotide reductase (RR) is essential for the reduction of ribonucleotides to deoxyribonucleotides utilized in DNA biosynthesis.[9,10] The X-ray structures of the reduced and oxidized form are known and the initial part of the chemical transformation catalyzed by the enzyme is shown in Scheme 1.6.



Scheme 1.6 Reaction of the reduced form of ribonucleotide reductase with O_2 to the oxidized form with concomitant formation of the tyrosyl radical.

The active site of the reduced form of ribonucleotide reductase contains two iron atoms bridged by two carboxylate groups. Furthermore there are two histidines coordinating to the dinuclear iron center and the remaining part of the coordination sphere is composed of carboxylate oxygen donor atoms. Interaction of the reduced form with oxygen generates, *via* two transient species, a tyrosyl radical and RR is converted to its oxidized form with an Fe(III)-Fe(III) oxo-bridge. The generated radical is reponsible for the reduction of ribonucleotides. The exact mechanism of the subsequent steps has not been elucidated yet.
Phosphohydrolases are known to have a dinuclear active site containing iron, zinc, manganese or magnesium and are capable of phosphate hydrolysis.[25] For instance, a dinuclear iron site is found in *mammalian purple acid phosphatases* (PAP) whereas the *kidney bean purple acid phosphatase* contains a heterodinuclear Fe(III)Zn(II) site. The PAP mediated hydrolysis occurs with inversion of the stereochemistry at phosphorus *via* a pentacoordinate intermediate, which is apparently stabilized by the metal ions and two histidines.[26] In the proposed mechanism, the phosphate ester is bound to M(II) [M(II) is Fe(II) or Zn(II)] and the Fe(III) bound hydroxide attacks the phosphate ester to form the intermediate (Scheme 1.7).



Scheme 1.7 Proposed mechanism for phosphate ester hydrolysis at the *kidney bean purple acid phosphatase* Fe(III)Zn(II) dinuclear site.

1.2.3 Dinuclear manganese enzymes

Compared to the copper and iron enzymes, dinuclear manganese enzymes are not explored extensively and the mechanisms are still speculative. A summary of dinuclear manganese enzymes and their functions is given in Table 1.1.[11] In enzymes the oxidation states of manganese appears to be restricted to Mn(II), Mn(III) and Mn(IV). Probably, manganese centers with oxidation states higher than Mn(IV) are too powerful oxidizing agents and therefore unlikely to appear in biological systems. Reactions catalyzed by dinuclear manganese active sites are redox reactions, (de)hydrations, isomerizations, (de)phosphorylation and phosphoryl transfer.

Table 1.1 Dinuclear manganese enzymes.[11]

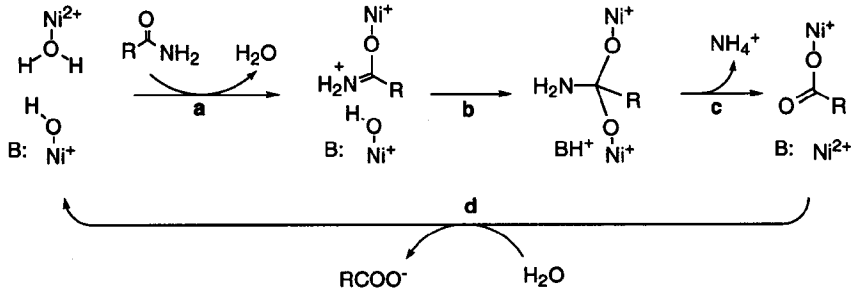
enzyme	Mn-Mn site[a]	reaction	enzyme reaction
arginase	Mn^{II}-X-Mn^{II}	arginine → urea + ornithine	hydration of guanidinium group
catalase	Mn^{II}-X-Mn^{II}, (3.6 Å)	$2H_2O_2 \rightarrow O_2 + H_2O$	redox, Mn^{II}, Mn^{III}
thiosulfate-oxidizing	Mn^{II}-X-Mn^{II}	$S_2O_3^{2-} \rightarrow SO_4^{2-}$	presumably redox
ribonucleotide reductase	presumed dinuclear Mn^{III}-O-Mn^{II}	ribonucleotides → deoxyribonucleotides	tyrosine → tyrosyl radical
xylose isomerase	$Mn^{II}(RCO_2)Mn^{II}$, (4.9 Å)	glucose → fructose	1,2-keto-alcohol isomerization
ribonuclease H	$Mn^{II}(RCO_2)Mn^{II}$, (4 Å) Mg or Mn	RNA + H_2O → cleaved RNA	phosphodiester hydrolysis

[a] Manganese-manganese distance in Å

1.2.4 Dinuclear nickel enzymes

Urease is an enzyme with a dinuclear nickel active site which catalyzes the hydrolysis of urea to ammonium carbamate.[25,27] The ligand environment of the nickel ions in the active site comprises nitrogen and oxygen ligands. The proposed mechanism[28] for the hydrolysis of urea is shown in Scheme 1.8.

The substrate (urea and a few substituted ureas and amides compounds) binds to one nickel (**a**), which is followed by nucleophilic attack by hydroxide (**b**) that is bound to the other nickel center to form a tetrahedral intermediate. This step (**b**) is supported by a general base which is proposed to be a histidine.[23] An active site cysteine, which is known to be present in the enzyme but not as a ligand to nickel, is proposed to act as general acid which promotes the release of ammonium ions (**c**) and the formation of a carboxylate or carbamate ion. Replacement of the coordinated carboxylate or carbamate ion by water leads to the regeneration of the initial state of the enzyme (**d**).

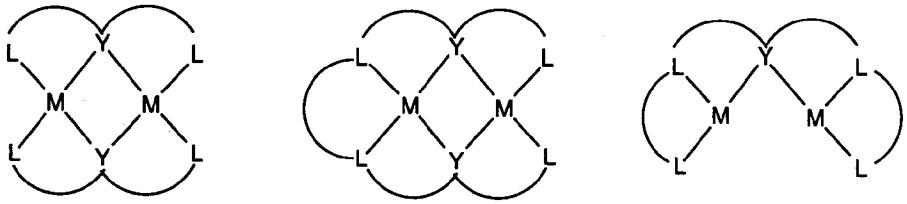


Scheme 1.8 Proposed mechanism for the hydrolysis of urea at the urease dinuclear nickel site.

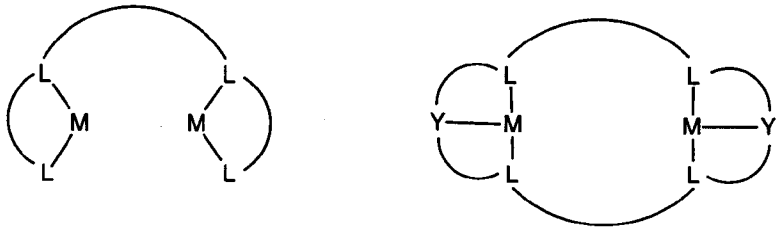
1.3 Synthetic dinuclear catalysts

1.3.1 Design of dinucleating ligands

For the synthesis of well defined dinuclear complexes, the choice of the ligand system is of major importance. Since 1970, investigations towards dinucleating ligands and related dinuclear complexes have increased significantly.[3] There are a number of conditions the dinucleating ligand has to satisfy. First of all, the ligand system has to be suitable to accommodate two metals. Moreover, the choice of the coordination environment is very important because it determines the nature of the metal ions (type of metals, oxidation states, homo- or heterodinuclear, bridging ligand features *etc.*) that can be bound. Finally, the metal-metal separation plays a crucial role in the activity of the designed complexes.
Dinucleating ligands can be divided in two classes (Fig. 1.2):[3d]
(*a*) Ligands which afford complexes in which the metal ions are sharing at least one donor atom. The ligands contain adjacent sites in which the central donor moiety provides a bridge between the metals. These ligands are termed compartimental ligands.
(*b*) Ligands which give rise to complexes in which donor atoms are not shared. In this case the donor sets are isolated.



Class (a) examples of dinuclear complexes of compartimental ligands



Class (b) examples of dinuclear complexes of ligands with isolated donor sets

Figure 1.2 Schematic representation of metal complexes of dinucleating ligands (M = transition metal and L, Y = donor atoms)

1.3.2 Reactivity of dinuclear catalysts

The catalytic activity largely depends on the structure of the complex.[29] The coordination environment does not only determine the nature of metal ions to be incorporated but, among other features, also the metal metal separation in the dinuclear complex.
The reactivity patterns of dinuclear complexes in which the two metals can cooperate are roughly divided into three classes (Figure 1.3). In the first class (a), the substrate is coordinated to both metal ions simultaneously. In this way, the substrate can be activated and react with another molecule, either bound to a metal or unbound. In the second class (b), the substrate is bound to one metal center and the reactant to the other. Activation of the substrate and reactant can lead to bond formation of these two molecules. In most enzymes discussed in Section 1.2, these two pathways of activation are often combined in one catalytic cycle. In the third class (not depicted in Figure 1.2), the second metal does not participate in the catalytic reaction, but helps to stabilize the reaction center for instance by donating or withdrawing electron density or by stabilizing a specific geometry at the dinuclear site. This is for instance proposed for the copper zinc dinuclear enzyme superoxide dismutase.
The optimum separation of the two metals is 3.5 - 6 Å. Even if there is no direct interaction between the metal ions, the metals are still close enough to enforce the interaction of the substrate with both metals (*a*) or to bind two reactants in close proximity (*b*).
Finally, another basic requirement of the catalyst is that the product must be readily released from the dinuclear binding site.

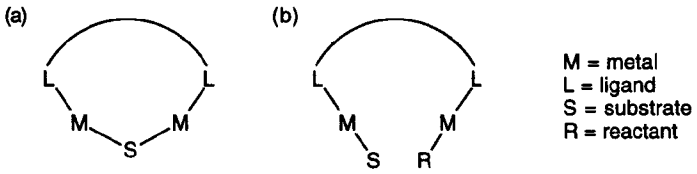


Figure 1.3 Schematic representations of possible cooperation of two metals in substrate (and reagent) activation.

1.4 Model systems for metallo-enzyme dinuclear active sites

1.4.1 Dinuclear copper complexes

Functional model systems of enzyme active sites are developed consisting of small, well defined molecules in order to mimic *e.g.* the formation of active intermediates, substrate binding and various aspects of the reactivity of enzymes. By mimicking the catalytic centers, it is possible to obtain more insight in the individual function of certain groups in the enzyme with respect to the reaction mechanism. The information can then be used in the development of new synthetic catalysts.
Dinuclear copper complexes and their dioxygen binding are widely studied for this purpose in attempts to mimic hemocyanin and tyrosinase active sites.[3,30] The metal-dioxygen complexes

found so far are very diverse in terms of structure, reactivity and spectral features and the different coordination modes are shown in Figure 1.4.

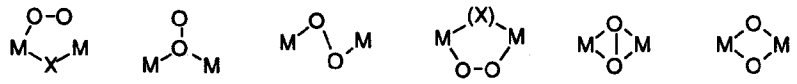


Figure 1.4 Coordination modes of dioxygen adducts adopted in dinuclear complexes.[30d]

Karlin and co-workers have developed a dinuclear copper complex, which is capable of binding dioxygen reversibly at low temperatures under formation of a deep purple compound **1.1** (Fig. 1.5).[31] Dioxygen is probably bound in a μ-1,1 way to one copper or alternatively in an unsymmetrical μ-1,2 mode to both coppers. The distance between the two copper centers is 3.3 Å. Furthermore, Karlin and co-workers reported on a mononuclear copper complex containing a tripodal tetradentate ligand, which showed self-assembly to a dinuclear *trans*-μ-1,2-dioxygen complex **1.2** upon reaction with dioxygen at -80 °C.[32] The dioxygen binding of the copper complexes **1.1** and **1.2** is only reversible at low temperatures, which is strikingly different from the reversible room temperature dioxygen binding of hemocyanin. Other copper(I) complexes that have been reported to form dioxygen complexes in solution are also subject to this instability in most cases.[33] However, recently an example of a dinuclear copper complex that is able to form a *trans*-μ-1,2-dioxygen complex at room temperature in protic media is found by Reedijk and co-workers.[34]

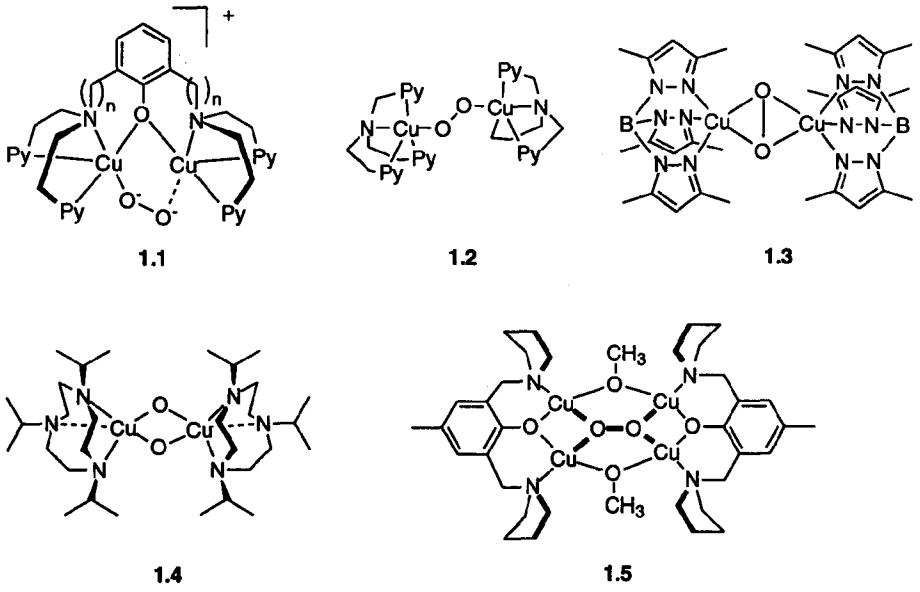


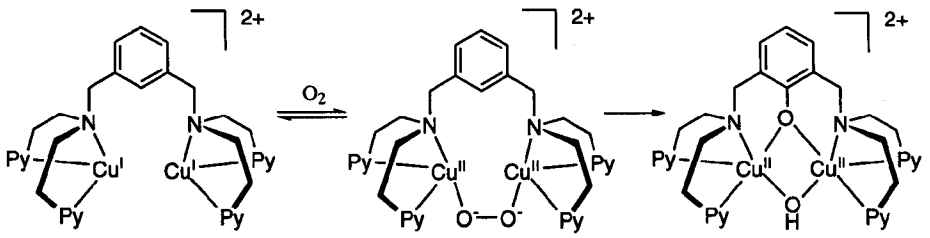
Figure 1.5 Dinuclear copper(II)-dioxygen complexes.

A breakthrough in copper dioxygen binding was made by Kitajima and co-workers by the synthesis of complex **1.3**.[35] X-ray crystallography showed that dioxygen is coordinated in a μ-η^2:η^2-peroxo mode with a copper-copper distance of 3.56 Å. The spectroscopic characteristics of **1.3** closely resemble those observed for oxy-hemocyanin and the discovery of **1.3** resulted in the final resolvement of the X-ray structure of *Limulus Polyhemus* oxy-hemocyanin.

A new type of copper-dioxygen complex was published by Tolman and co-workers.[36] This complex **1.4** contains a $Cu_2(\mu\text{-}O)_2$ core as was found by X-ray crystallography. Important features are the copper-copper distance of 2.79 Å in **1.4** and the oxygen-oxygen distance of 2.28 Å, which are significantly different from the values found for the $Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)$ core (3.56 and 1.41, respectively). The synthesis of complex **1.4** containing a $Cu_2(\mu\text{-}O)_2$ core is performed in THF and is dependent on the solvent. By using another solvent (CH_2Cl_2) a $Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)$ core is formed and interconversion between the two different oxygen binding modes is possible upon change of solvent.

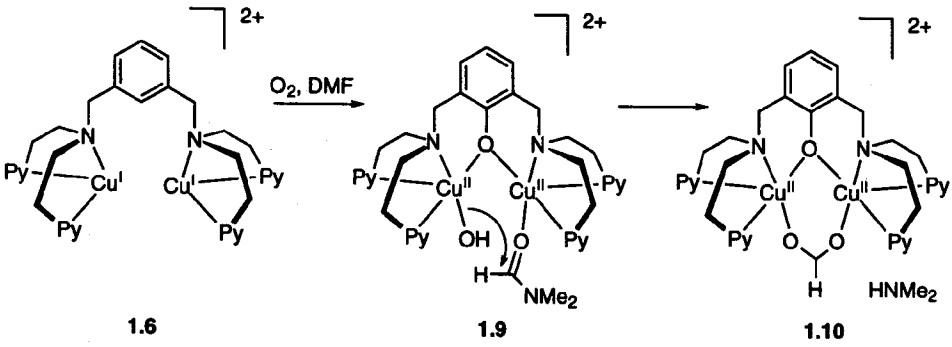
The peroxo-copper complex **1.5** with an unsual μ_4 mode of coordination of the peroxo ligand has been reported by Krebs and co-workers.[37] In this complex **1.5** the peroxo ligand is coordinated end-on in a fourfold bridging μ_4-$(\eta^1)_4$ mode and lies above the Cu_4 plane. Another interesting structural feature is the ClO_4 unit (not depicted in structure **1.5**) which is situated below the Cu_4 plane and the oxygen atoms of ClO_4 are indentically bound to all the four copper ions.

Dinuclear copper complex **1.6** showed arene hydroxylation upon reaction with dioxygen to provide **1.8** (Scheme 1.9).[31] The reactivity of this copper complex resembles the reactivity of tyrosinase. Related work on O_2 binding with dinuclear complexes, oxygenation and mechanics studies have been reported from our group and by others.[38]



Scheme 1.9 Tyrosinase model system.

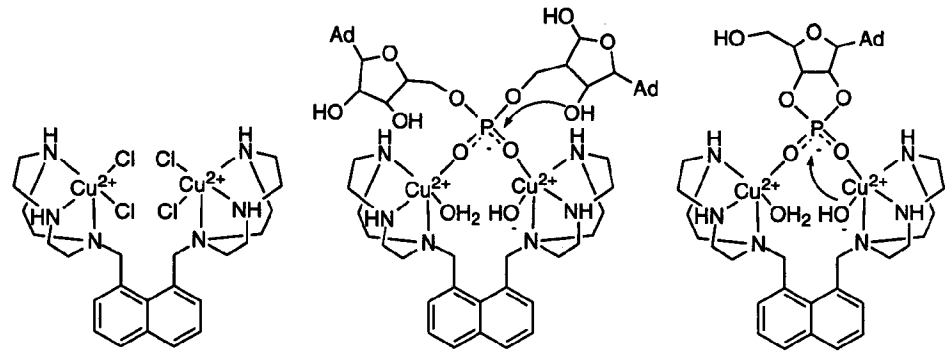
A few years ago, a biomimetic model system for amide hydrolysis was reported by Karlin and co-workers.[33b,39] Complex **1.6** reacts with dimethylformamide instantaneously to form **1.10** (Scheme 1.10). In the postulated mechanism, the carbonyl group of the amide is activated by one copper center while a hydroxide is transferred by the second copper center as shown in structure **1.9**. Recently, Karlin and co-workers have reported on a dinuclear copper complex that is capable of facile hydrolysis of unactivated esters and hydration of acetonitrile.[40]



1.6 1.9 1.10

Scheme 1.10 Biomimetic system for the hydrolysis of amides.

Dinuclear copper complex **1.11**, developed by Chin and co-workers, is capable of the hydrolysis of RNA (Fig. 1.6).[41] The cooperativity of the two metal centers is presumably due to bridging of the phosphate ester between the two copper centers. This binding mode of phosphate esters is also seen in previously reported dinuclear copper and cobalt complexes.[42] In the proposed mechanism the 2-hydroxy group acts as an intramolecular nucleophile (see structure **1.12**), which is followed by the hydrolysis of the phosphate ester by a copper bound hydroxide (see structure **1.13**). The dinuclear copper complex is 300-500 times more active than the corresponding mononuclear complex (1,4,7-triazacyclononane)copper(II) dichloride.



1.11 1.12 1.13

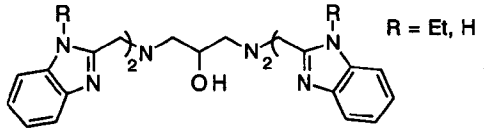
Figure 1.6 Hydrolysis of RNA by a dinuclear copper complex.

Recently, a heterodinuclear Co(II)-Cu(I) complex has been reported by Collman and co-workers[43] as a model for Cytochrome c oxidase, which catalyzes the four electron reduction of O_2 to H_2O. This dinuclear complex consists of a cobalt porphyrin with a Cu(I) triazacyclononane attached at one side and an imidazole on the other side of the porphyrine ring. The bimetallic complex strongly binds oxygen in a 1:1 stochiometry as indicated by IR

and mass spectrometry. Furthermore, a four electron reduction of O_2 was observed at physiological pH.

1.4.2 Dinuclear iron complexes

The dioxygen activation by dinuclear iron active sites in enzymes is fascinating. While hemerythrin binds dioxygen reversibly, ribonucleotide reductase and methane monooxygenase bind dioxygen irreversibly and are capable of oxidizing tyrosine and hydrocarbons, respectively. Until now, only a few dinuclear iron model systems are known that bind (reversibly) dioxygen.
Que and co-workers have used dinucleating ligand **1.14** with a 2-hydroxypropane backbone to prepare dinuclear iron complex **1.17** (Fig. 1.7).[44] Complex **1.17** is able to bind dioxygen irreversibly by forming a 1:1 O_2 adduct. Suzuki and co-workers found that by using ligand **1.15**, the corresponding dinuclear iron complex binds dioxygen reversibly below -35 °C.[45] However, the related complex without the methyl groups at the 6-position of the pyridines binds dioxygen irreversibly. Probably, the 6-methyl groups introduce a steric effect that results in a shift of the Fe^{III}/Fe^{II} potentials to more positive values, thereby favouring an equilibrium between the deoxy and oxy forms.



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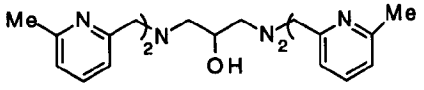

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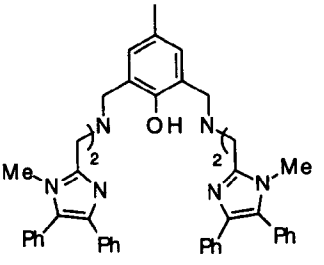

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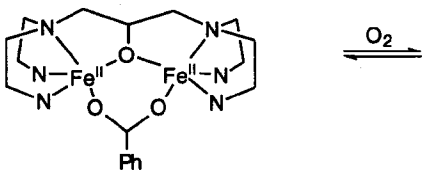
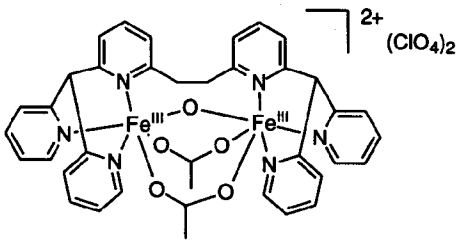


1.17 **1.18**

Figure 1.7 Dinucleating ligands and iron complexes capable to bind dioxygen.

Recently, Suzuki and co-workers have reported on dinuclear iron complex **1.17** derived from ligand **1.16**, that can form a very stable oxygen adduct **1.18**.[46] X-ray crystallography and Mössbauer data for this complex show two distinct high spin iron(III) centers, in which oxygen is bound in an *cis*-μ-1,2 mode. The two iron centers have a distorted octahedral coordination geometry. X-ray structure analysis of the dioxygen adduct of the dinuclear iron complex of ligand **1.14**, to which triphenylphosphine oxide was added to achieve stability, showed a similar *cis*-μ-1,2 fashion of oxygen binding but did not show two different iron centers.[47] Another X-ray structure of a *cis*-μ-1,2 dioxygen adduct has been reported by Kim and Lippard.[48]

A very reactive dinuclear iron complex **1.19**, of a dinucleating hexapyridine ligand, was published by Kodera and co-workers which mimics MMO (Fig. 1.8).[49] This complex gave a very rapid functionalization of alkanes with *m*-chloroperbenzoic acid. For the conversion of cyclohexane to cyclohexanol, the system showed a high turnover frequency of 70 [mol product. mol catalyst^{-1}. min^{-1}] and a turnover number of 164 [mol product. mol catalyst^{-1}]. Other products formed during this reaction are cyclohexanone (68 turnovers), ε-caprolactone (48 turnovers) and chlorocyclohexane (12 turnovers). Upon renewed addition of *m*-chloroperbenzoic acid no loss of activity was found.

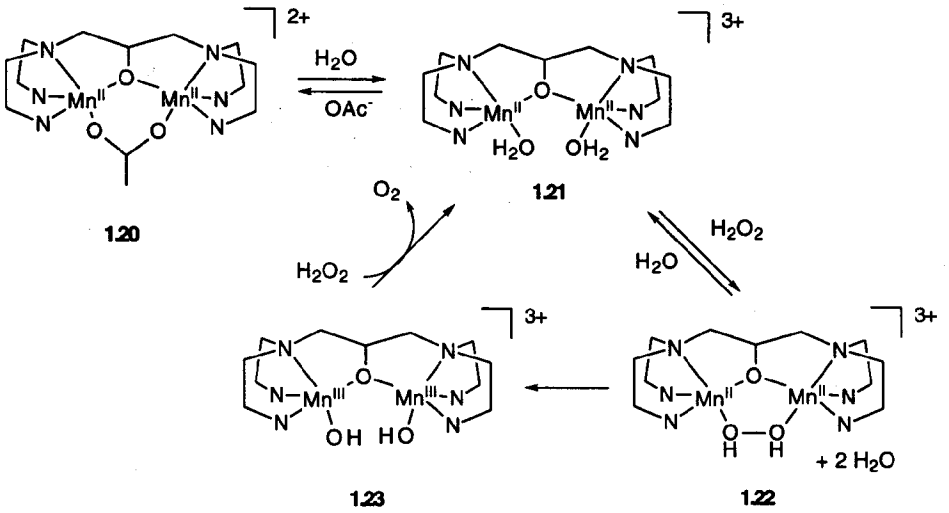


1.19

Figure 1.8 A dinuclear iron catalyst that show MMO type activity.

1.4.3 Dinuclear manganese complexes

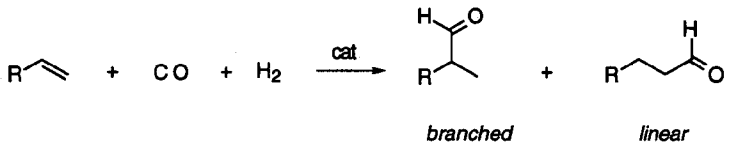
The disproportionation of hydrogen peroxide into water and dioxygen is catalyzed by the enzyme catalase. A dinuclear manganese complex **1.20** based on heptadentate ligand **1.14** was reported by Dismukes and co-workers as a mimic for catalase.[50] In the postulated mechanism, dinuclear manganese complex **1.20** gives the "active" form of the Mn(II), Mn(II) catalyst **1.21** *via* an equilibrium with water, possibly by dissociation of the μ-acetate (Scheme 1.11). In the second step, hydrogen peroxide binds to **1.21** by displacement of bound water yielding **1.22**. This is followed by intramolecular electron transfer in which both Mn(II) are oxidized to Mn(III) with concomitant peroxide reduction to hydroxide leading to **1.23**. Subsequently reduction by a second peroxide molecule yields O_2 and restores the active starting material. Other dinuclear manganese biomimetic complexes are reviewed by Que and True[51] and by Hage.[52]



Scheme 1.11 Proposed mechanism of catalase activity by dinuclear manganese complex **1.20**.

1.5 Dinuclear rhodium catalysts

An important breakthrough in dinuclear catalysis, not focusing on biomimetic systems, has been achieved by Stanley and co-workers with a dinuclear rhodium catalyst for the hydroformylation of α-olefins.[13] In the hydroformylation reaction, alkenes react with hydrogen and carbon monoxide to give either linear (*l*) or branched (*b*) aldehydes (Scheme 1.12). Dinuclear rhodium complex, *rac*-$[Rh_2(nbd)_2(et,ph\text{-}P4)]^{2+}(BF_4)_2$ (nbd = norbornadiene) **1.24** is a precursor for a highly active and regioselective catalyst in which the two rhodium centers showed cooperativity of the two metal centers in the hydroformylation reaction (Fig 1.9). The hydroformylation of 1-hexene catalyzed by **1.24** is about 40% faster then the commercial Rh/PPh_3 catalyst and gives a high linear to branched aldehyde ratio (*l*/*b* = 28).



Scheme 1.12 Hydroformylation reaction of α-olefins.

It is proposed that the key step in the catalytic cycle is an intramolecular hydride transfer from one rhodium center to the other which contains the acyl chain, yielding the aldehyde. To verify the hypothesis of an intramolecular hydride transfer, two ligands were prepared in

which the rhodium atoms are unable to get close to one another. In complexes **1.25** and **1.26** the ethylene spacer is replaced by a rigid *p*-xylylene spacer and a more flexible propylene spacer, respectively. Furthermore, a mononuclear complex **1.27** was examined. All these models either do not catalyze the hydroformylation or catalyze the hydroformylation with very low activity. Recent *in situ* FTIR and NMR studies indicated that the mechanism is more complicated than initially proposed. The presumed active catalyst in the hydroformylation is based on complex **1.28** containing a unique Rh(II)-Rh(II) bond.[13b] This represents an 18-electron Rh(II) complex with an edge sharing bioctahedral structure, which is extremely rare. A feature of this complex is a very large $^1J_{Rh\text{-}H}$ coupling constant of 164 Hz.

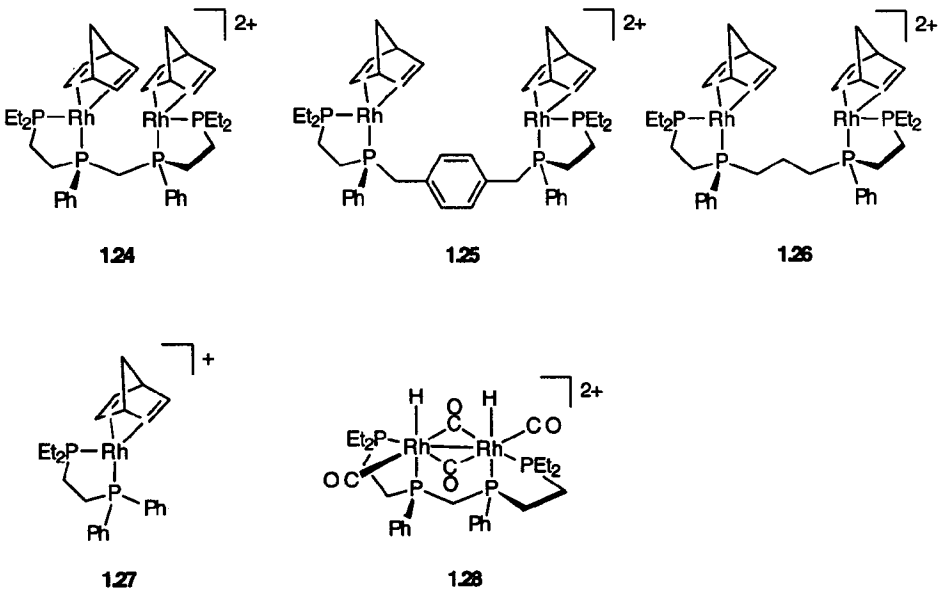


Figure 1.9 Mono- and dinuclear rhodium complexes developed by Stanley and co-workers.

The high linear aldehyde selectivity is attributed to the rigid dinuclear structure of **1.28** and the favorable steric effects at the dinucleating phosphine ligand et,ph-P4. Coordination of an alkene to a typically mononuclear square planar rhodium phosphine catalyst causes the other ligands to bend away to form a trigonal bipyramid (or square pyramid). This reduces the steric effectiveness of the phosphor ligands for the insertion of the alkene in the rhodium hydride bond in such a way that the desired linear rhodium alkyl species is formed. In catalyst **1.28**, the alkene coordination cannot distort the steric effectiveness of the ligands since the Rh-Rh bond and the bridging carbonyls allow only a minimum of ligand reorganization. Due to the steric effect of the et,ph-P4 ligand, the alkene insertion in the M-H bond is directed to form a linear alkyl group resulting in a linear aldehyde.
Another type of dinuclear rhodium complexes, $Rh_2(\mu\text{-}SR)_2(CO)_2L_2$ (L = PPh_3) have been published by Kalck and co-workers.[53] It is proposed that these dinuclear rhodium complexes catalyze the hydroformylation reaction also *via* a dinuclear mechanism.

1.6 Heterobimetallic systems

Cooperation of two metals in a heterobimetallic system is an attractive approach because the two metals can perform different tasks. Most often a hard and a soft metal are combined in one complex as the incorporation of a hard metal center, for instance a Lewis acid site, into a soft mononuclear transition metal catalyst may greatly alter the reactivity and selectivity. This has been demonstated for Rh-Ti and Rh-Zr complexes in the hydroformylation reaction of olefins.[54] It is proposed that the reaction proceeds mainly *via* the rhodium center and that the second metal is able to increase or decrease the electron density at the rhodium center during the catalytic cycle. Another heterobimetallic complex which showed similar cooperativity is a compound of the type $[H(CO)(PPh_3)_2Ru(\mu\text{-bim})M(cod)]$ (bim = 2,2'-biimidazolate, cod = 1,5-cyclooctadiene, M = Rh, Ir). These dinuclear catalysts show approximately 30 times higher activity in the hydrogenation reaction of cyclohexene than the parent mononuclear compounds $[RuH(Hbim)(CO)(PPh_3)_2]$ and [M(Hbim)(cod)].[55]
Kagan and co-workers and Jacobsen and co-workers have simultaneously published a chiral bimetallic catalyst **1.29** derived from modified diop (2,3-*O*-isopropylidene-2,3-hydroxy-1,4-bis(diphenyl)phosphinobutane).[56] The bimetallic complex contains a rhodium diphosphine unit, which acts as catalytic center in hydrogenation and hydrosilylation reactions and an arylboronic ester to function as a Lewis acid binding site for amines (Fig. 1.10). Binding studies showed that the rhodium boron dinuclear complex **1.29** can bind amino olefins, as is illustrated in structure **1.30**, in which the two functionalities are more than 3 methylene groups apart.
The hydrogenation reaction of *N*-acetyldehydrophenylalanine and the methyl ester of *N*-acetyldehydrophenylalanine catalyzed by rhodium boron complex **1.29** gave high yields but it was slightly less stereoselective than hydrogenation with the mononuclear diop rhodium catalyst **1.31**. Also in the hydrosilylation reaction of ketones lower *ee*'s were obtained for the rhodium boron complex **1.29**.

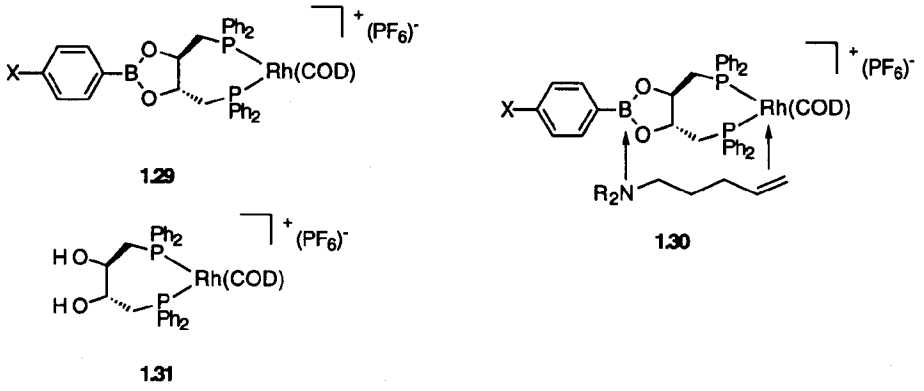
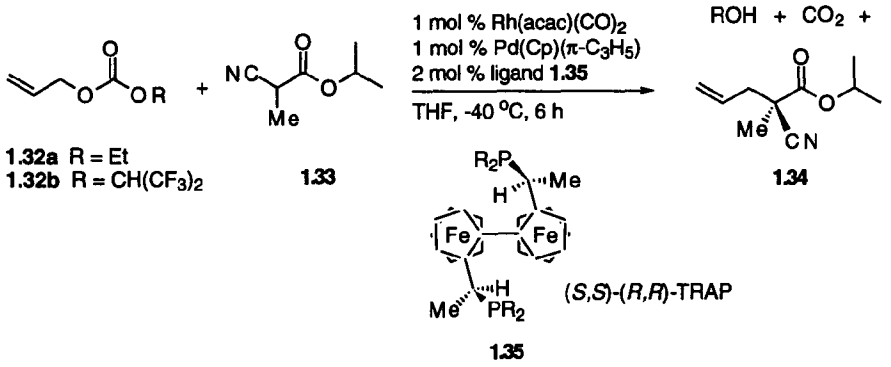


Figure 1.10 Bimetallic catalyst with a rhodium active site and a boron Lewis acid binding site.

In contrast, using lanthanides in combination with early transition metals, impressive results have been obtained by Shibasaki and co-workers with a new class of heterobimetallic compounds. The new catalysts consist of a central metal ion (*e.g.* La^{3+}, Al^{3+}), three alkali metal ions (*e.g.* Li^+, Na^+, K^+) and three molecules of 1,1'(*R*)- or 1,1'-(*S*)-binaphthol (BINOL). In the asymmetric nitroaldol addition with a LaLi-BINOL compound as catalyst up to 94% enantiomeric excess and 90% yield were obtained.[57] In the asymmetric hydrophosphonylation reaction of imines and aldehydes, a LaK-BINOL catalyst gave enantiomeric excesses up to 96% with yields of 70%.[50c] Furthermore, in the Michael addition, the highest enantiomeric excess (95% *ee*, quantitative yield) was achieved with a LaNa-BINOL catalyst.[58] Mechanistic studies showed that the lanthanide functions as a Lewis acid center to activate the enone as well as to control the geometry of the coordinated enone.

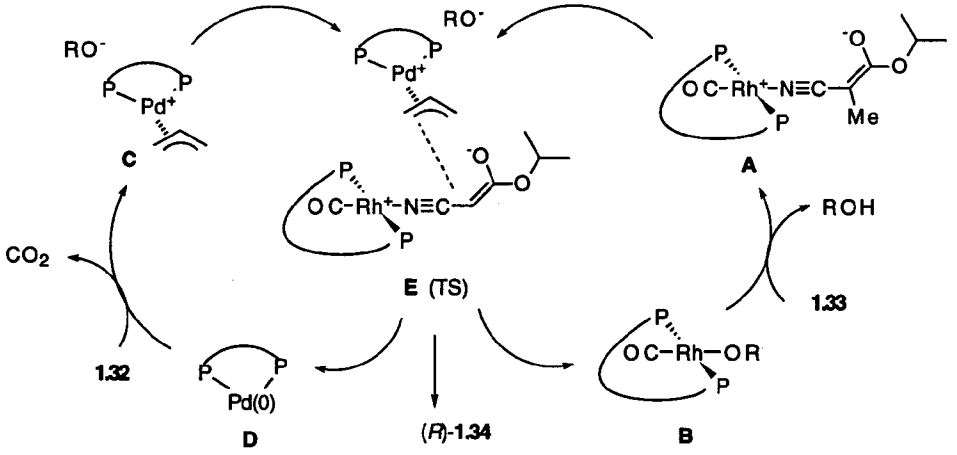
1.7 Two-component catalyst systems

Two-component catalyst systems consist of two different transition metal complexes, in which the two catalysts activate their respective substrates resulting in a more active system compared to the mononuclear complexes. Hidai and co-workers have reported several bimetallic catalysts including a $Co_2(CO)_8$-$Ru_3(CO)_{12}$ system for the hydroformylation of olefins[59] and the $PdCl_2(PPh_3)_2$-$Ru_3(CO)_{12}$ for formylation of aryl iodides and vinyl iodides which are twice as active as the mononuclear system.[60] In the proposed mechanism, the synergistic effects are explained by dinuclear reductive elimination reactions between acylcobalt or acylpalladium intermediates and hydridoruthenium to give the corresponding aldehydes. Based on the same principle a Pd-Co system was developed for the carbonylation of aryliodides with $HSiEt_3$.[61]
Recently, Sawamura and co-workers reported an impressive example of a two component rhodium palladium catalyst.[62] The *trans* chelating bisphosphine ligand (S,S)-(R,R)-TRAP was applied in combination with $Rh(acac)(CO)_2$ and $Pd(Cp)(\pi\text{-}C_3H_5)$ in the enantioselective allylic alkylation of α-cyano esters (Scheme 1.13).



Scheme 1.13 Enantioselective allylic alkylation of an α-cyano ester promoted by a two-component Rh-Pd catalyst and a chiral ligand.

The proposed mechanism is shown in Scheme 1.14. The π-allylpalladium complex[63] **C** can be produced from TRAP, an allylic carbonate and a catalytic amount of a palladium complex. The rhodium-enolate complex **A** is initially formed from $Rh(acac)(CO)_2$, TRAP and cyanoester **1.33**. Nucleophilic attack of the enolate **A** on the π-allylpalladium complex **C** proceeds *via* transition state **E** and produces (*R*)-**1.34** in high yields (84-98%) and with an enantiomeric excess up to 99%. At this step, the palladium(0) complex **D** is regenerated and the alkoxide (RO^-) becomes a ligand for rhodium to form alkoxy rhodium(I) complex **B**. When in this reaction palladium was omitted, no conversion was observed after 24 h. Conversily, when rhodium was left out, high yields were obtained but no enantiomeric excess was found. These results together shows the unique cooperative features of this system.



Scheme 1.14 Proposed mechanism for the enantioselective allylic alkylation catalyzed by a two-component Rh-Pd system.

1.8 Conclusions

Considerable progress is seen in recent years in approaches to bimetallic catalysis and some remarkable discoveries on enhanced selectivity and/or activity show potential benefits of dinucear catalysts. A number of dinuclear complexes has been investigated in order to activate small molecules. It is evident that dioxygen binding with synthetic dinuclear copper and iron systems has considerable impact on our understanding of dioxygen binding in natural systems. Furthermore copper, iron, cobalt and manganese complexes have shown interesting catalysis in attemps to design mimics of enzymes. The cooperativity of the two rhodium atoms observed in the hydroformylation reaction (Section 1.5) demonstrates that dinuclear catalysis might provide new opportunities for many other areas of catalysis not related to enzymic mimics. In heterobimetallic systems, an enhancement of the activity can be obtained by using a second metal which can control electron density at the catalytic center. Finally, during the catalytic cycle two-component systems based on two different transition metal

complexes have shown cooperativity in dinuclear catalysis. For instance, a two-component rhodium palladium system gave excellent catalytic activity with high enantioselectivity in the alkylation of activated nitriles. These two component systems can be used in future to design new dinuclear catalysts.

1.9 Aims and outline of this thesis

This thesis describes the synthesis and characterization of new dinuclear complexes and their application in bimetallic catalysis. Compared to biomimetic copper, iron and manganese systems, dinuclear catalysts based on palladium, platinum, rhodium and nickel have received limited attention. It is a challenge to synthesize dinuclear complexes of these metals and to study their activity in hydrogenation, hydroformylation and C-C coupling reactions in order to establish whether faster or more selective reactions can be achieved. Therefore, we developed different types of ligands, compartimental ligands as well as ligands with isolated donor sets, and studied their complexation behaviour, as well as their catalytic activity.
In Chapter 2, mono- and dinuclear complexes based on phosphorus nitrogen ligands are introduced. Phosphorus-nitrogen ligands are known to coordinate in an unique way to palladium, platinum, rhodium and nickel and this structural feature is explored in new dinuclear complexes. The phosphorus atom coordinates strongly to late transition metals while the nitrogen atom binds more weakly.[64] Both symmetrical ligands as well as dinucleating ligands which are non-symmetrical are described. The latter ones are compartimental ligands (Section 1.3.1) and have an additional donor atom. Lack of symmetry creates different chemical environments for the two metals, which is often found in the dinuclear metals sites of metalloenzymes.
Chapter 3 also deals with compartimental ligands in which the bridging donor atom holds the two metals at a fixed distance of one another. The backbone is based on 1,3-diaminopropanol and the donor atoms of the dinucleating ligand are two phosphorus, two nitrogen and 1 oxygen atom. Dinuclear complexes of palladium, rhodium and nickel were synthesized and characterized. Furthermore, a heterobimetallic rhodium-palladium complex has been described. The catalytic activity of these complexes has been tested in hydrogenation, hydroboration and hydrosilylation reactions.
In Chapter 4, phosphorus-nitrogen ligands based on a biphenyl backbone are described. From these types of ligands mononuclear as well as dinuclear complexes were synthesized. Because of the flexibility of the biphenyl backbone, the metal metal distance is variable in solution in contrast to the systems described in Chapter 3.
Dinuclear catalysts based on rhodium phosphite complexes are the subject of Chapter 5. The complexes have been studied extensively with NMR spectroscopy and X-ray crystallography. The dinuclear complexes and the corresponding mononuclear complexes were examined as catalysts in the hydroformylation reaction.
Chapter 6 discusses ethylene oligomerization catalyzed by mononuclear palladium complexes. The study of dinuclear complexes based on phosphorus-nitrogen ligands (Chapter 3 and 4) led to the discovery of interesting reactivity of the corresponding mononuclear iminophosphine palladium complexes. The steric and electronic factors governing these

iminophosphines as ligands were studied in the palladium catalyzed oligomerization of ethylene.

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